

Application Serial No.: 10/039,876
Amendment dated: January 5, 2006
Response to Office Action dated: July 5, 2005

Amendments to the Specification:

Please replace the paragraph beginning at page 6, line 15, with the following amended paragraph:

~~The~~ Figure 1 illustrates a multiple alignment of murine EF-7 protein (MMU72677_1), human 2-19 protein (219_HUMAN), human D87120 (D87120_1_|), and z219a (z219a.pep).

Please replace the paragraph beginning at page 13, line 30, with the following amended paragraph:

The nucleotide sequence of full-length z219a is described in SEQ ID NO. 1, and its deduced amino acid sequence is described in SEQ ID NO. 2. The multiple alignment (Figure 1) revealed that z219a is a member of a family of proteins that are characterized by their signal sequence, predicted small size (15-40 kD), tissue-specific expression, certain novel motifs disclosed herein, glycosylation sites, and lack of long hydrophobic segments, suggesting a small secreted molecule with potential as a new class of secreted cytokine-like molecules.

Please replace the paragraph beginning at page 14, line 4, with the following amended paragraph:

Analysis of the DNA encoding z219a polypeptide (SEQ ID NO:1) revealed an open reading frame encoding 235 amino acids (SEQ ID NO:2) comprising a predicted signal peptide of 25 amino acid residues (residue 1 (Met) to residue 25 (Gly) of SEQ ID NO:2), and a mature polypeptide of 210 amino acids (residue 26 (Tyr) to residue 235 (Ser) of SEQ ID NO:2). Multiple alignment of z219a with other

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members of the human 2-19 protein family revealed the following 3 regions of conserved amino acids (see Figure 1):

Please replace the paragraph beginning at page 88, line 13, with the following amended paragraph:

The excised DNA was subcloned into plasmid CEEpZP9 which had been cut with BamHI and EcoRI. The z219aCEE/pZP9 expression vector uses the native z219a signal peptide and attaches the Glu-Glu tag (SEQ ID NO:21) to the C-terminus of the z219a polypeptide-encoding polynucleotide sequence. Plasmid pZP9 (deposited at the American Type Culture Collection, ~~12301 Parklawn Drive, Rockville, MD~~, 10801 University Boulevard, Manassas, VA 20110-2209 ATCC No. 98668) is a mammalian expression vector containing an expression cassette having the mouse metallothionein-1 promoter, multiple restriction sites for insertion of coding sequences, a stop codon and a human growth hormone terminator. The plasmid also has an *E. coli* origin of replication, a mammalian selectable marker expression unit having an SV40 promoter, enhancer and origin of replication, a DHFR gene and the SV40 terminator.

Please replace the paragraph beginning at page 72, line 34, with the following amended paragraph:

The z219a gene is located at the 21q22.3 region of chromosome 21. Trisomy 21, one of the most common chromosomal abnormalities, causes Down Syndrome (Penrose, L.S., J. Genet. 27:219, 1933; Hook, E.G., J. Am. Med. Assoc. 249:2034-2038, 1983). Moreover, the Down Syndrome critical region is the 21q22.3 locus of chromosome 21. Thus, since the z219a gene maps to this critical region, the z219a polynucleotide probes of the present invention can be used to detect Down Syndrome trisomy or partial

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trisomy (Rahmani, Z. et al., Proc. Nat. Acad. Sci. 86:5958-5962, 1989; Delabar, J.M. et al., Europ. J. Hum. Genet. 1:114-124, 1993). Moreover, several genes of known function map to this region. For example, the trefoil factors map to the 21q22.3 region, as discussed herein. Moreover, amongst other genetic loci, those for Knobloch Syndrome (21q22.3); collagen IV (alpha-1 and -2) and collagen VIII alpha-1 (21q22.3); integrin beta-2 (21q22.3); interferon receptors (21q22.1); and familial platelet disorder (21q22.1-q22.2), all manifest themselves in human disease states as well as map to this region of the human genome. See the Online Mendellian Inheritance of Man (OMIM) gene map, and references therein, for this region of chromosome 21 on a publicly available WWW server (~~http://www3.ncbi.nlm.nih.gov/htbin-post/omim/getmap?chromosome=21q22.3~~). All of these serve as possible candidate genes for an inheritable disease which show linkage to the same chromosomal region as the z219a gene.

Please replace the paragraph beginning at page 86, line 13, with the following amended paragraph:

Z219a was mapped to chromosome 21 using the commercially available "GeneBridge 4 Radiation Hybrid Panel" (Research Genetics, Inc., Huntsville, AL). The GeneBridge 4 Radiation Hybrid Panel contains DNAs from each of 93 radiation hybrid clones, plus two control DNAs (the HFL donor and the A23 recipient). A publicly available WWW server (~~http://www.genome.wi.mit.edu/cgi-bin/contig/rhmapper.pl~~) allows mapping relative to the Whitehead Institute/MIT Center for Genome Research's radiation hybrid map of the human genome (the "WICGR" radiation hybrid map) which was constructed with the GeneBridge 4 Radiation Hybrid Panel.

Application Serial No.: 10/039,876
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Please replace the paragraph beginning at page 87, line 13, with the following amended paragraph:

The results showed that z219a maps 210.83 cR_3000 from the top of the human chromosome 21 linkage group on the WICGR radiation hybrid map. Proximal and distal framework markers were D21S1826 and D21S266, respectively. The use of surrounding markers positions z219a in the 21q22.3 region on the integrated LDB chromosome 21 map (The Genetic Location Database, University of Southampton, ~~www~~ server, ~~http://cedar.genetics.soton.ac.uk/public_html/~~ United Kingdom) .